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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1653	

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,382	SETO ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *Japan 10/274574* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' claim for foreign priority under 35 U.S.C. 119 (a)-(d) in the declaration is acknowledged. Preliminary amendment filed 29 March 2001 prior to patent examination as to amendment of claims 3, 6, 7, 9 and 10 and addition of new claims 12-16 has been entered. Thus, Claims 1-16 are pending. Applicants have provided a copy of the priority document: Japan 10/274574 filed 29 September 1998; however, applicants do not submit the corresponding translation for the document which is required for full consideration of the claimed foreign priority.

Election/Restrictions

Applicant's election with traverse of Group II, Claims 4-10 and 13-16, filed 30 August 2002 (Paper No. 11) is acknowledged. The traversal is on the ground that the claim of one invention is indivisible from claim of the other invention. This is not found persuasive because the following reasons.

Applicants argue that Groups I and II contain linking claims; Claim 3 in Group I, is indivisible from Claim 7, in Group II, because the method of Claim 3 cannot be practiced without the substance of Claim 7 and the method of Claim 7. The argument is unpersuasive because (i) non-elected Claim 3 does not require the substance for practicing the method of Invention I (Group I) as the invention is drawn to controlling granule secretion as opposite to Invention II (Group II) that requires the substance since the invention is directed to detecting the substance which inhibits or activate a granule secretion; and (ii) Claim 7 *per se* does not recite the substance.

The concerns in applicant traverse and election (30 August 2002) pages 1-2 are unpersuasive. As to item 1, applicants assert that Claim 3 needs the substance of Claim 7. This is unpersuasive because detecting a substance that affects granule secretion does not automatically result in control of granule secretion. As to Group I, the claim starts with calcium binding myeloid-associated calgranulin proteins that exhibit activity of increasing granule secretion whereas in Group II, the concept is to find a compound/a target substance (see page 27, lines 9-10) that would have affected the calgranulin-associated active granule secretion. There is also a fundamental difference in the required search, and art anticipating and/or making obvious over one of the inventions would not necessarily have rendered the other invention obvious or anticipated.

Applicants further assert that Group III is indivisible from Group I (see page 2 of the response). This is found not persuasive because Group I recites no substance of modulating granule secretion. As the same reason stated foregoing, method of Group I and method of Group III is patentably distinct from each other with respect to ingredients (Group I comprising SEQ ID NO: 1 and SEQ ID NO:2 polypeptides whereas Group III comprising a substance for both controlling intimal injury of blood vessels and inhibiting granule secretion), method steps, targets, outcome. Therefore, restriction are necessary, i.e., separate classification, status, or field of search.

Upon due reconsideration, previously withdrawn claims are rejoined and the requirement for restriction withdrawn. Claims 1-16 are examined in this Office Action.

Specification Objections

The disclosure is objected to because of the following informalities:

In page 2, line 22, the term "themechanism" should be changed to "the mechanism".

In page 11, line 29, "HEPES" should be spelled out in full at the first instance of use. See also, page 11, line 27, "MEM"; and page 12, line 26, "KV";

In page 36, lines 12-15, the recitation "...compound 1 and compound 2 increased... remarkably increased" is not apparent because according to data shown on Table 1, both compound 1 and compound 2 exhibit inhibitory effects on lactoferrin secretion; thus, the recitation "increased" in lines 13 and 15 is advised to changed to "decreased" instead.

In page 9, lines 25-25, "the amino acid sequence 1-93 of Sequence ID No. 1 of..." should be changed to "the amino acid sequence 1-93 encoded by SEQ ID NO:1 of..." because SEQ ID NO: 1 as recited is a polynucleotide sequence not a peptide sequence. The same changes should be made throughout the specification for clarity.

In page 16, line 8, "base sequence" should be changed to "polynucleotide sequence".

In Claim 4, item B), the article "the" in the recitation "the step A" should be deleted.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1- 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "active form of calgranulin"; it not clear as to whether or not the said active form refers to calgranulin binding calcium ion, or calgranulin forming a heterodimer that acts as an active functional unit (see Hessian, P. A. (2001) *Eur. J. Biochem.* 268, 353-363, wherein MRP-8 is calgranulin A and MRP-14 is calgranulin B), or phosphorylated calgranulin that display increased calcium binding compared to nonphosphorylated forms (see page 353 of Hessian et al. reference as cited above), or undefined functional activity of calgranulin. Note that calgranulins A, B and C are members of the S100 protein family that are specifically expressed in neutrophils and monocytes. Their functions have not been clearly defined, but they are known to bind calcium. Porcine calgranulin C has been shown to undergo conformational change upon calcium binding and has been implicated in Ca^{2+}-dependent signal transduction pathways while human calgranulin C has been shown to translocation to the polymorphonuclear neutrophils plasma membrane, together with calgranulins A and B during stimulation of the cell by Ca^{2+}-dependent stimuli. With the concerns stated above, therefore, the recitation "active form" is indefinite. Claims 3, 4, 5, 7, 14 and 15 are also rejected as not clarify the issue. The dependent claims are included in the rejection.

Claim 2 is indefinite as to the definition and properties of "neutrophil-like culture cells"; are or are not the neutrophil cells? If not, what is the cell type. See also Claims 6 and 13.

Claim 3 is indefinite as to the amino acid sequences of 1-93 of SEQ ID NO: 1 (please change Sequence ID No.1 to SEQ ID NO:1) since SEQ ID NO:1 is a DNA sequence. In item (i) the "Sequence Table" is indefinite as to the table (tables should not per se be referenced to in the claim), or, was the terminology meant to refer to the sequencing listing? If so, the "of the Sequence Table" can be deleted from the claim. Item (i) should also make clear to what the "and binding calcium" refers. Is it the peptide that binds calcium or is it the peptide and calcium or is there a step of binding the calcium and the peptide? See also item (ii) and (iii) as to both of the above issue as well as claims which depend on claim 7 and which do not clarify the above issue. See also Claims 7, 12 and 14-16.

Claim 4 is indefinite as to the recitation (see item B) "before, after, or during the step A". it is presumed that steps occur in the order listed thus step B should be practiced during or after not before. Further, Claim 4, item B) recites "the mixture" which lacks antecedent basis; and is unclear as to whether or not the said mixture refers to: (i) a complex of calcium compound with calgranulin peptide(s), or (ii) heterodimer form (a "mix") of calgranulins, e.g. calgranulin A-calgranulin B heterodimer, or (iii) an admixture of calcium compound-calgranulin complex with a vehicle molecule that is responsible for transferring the complex into target cell, e.g. liposome, or (iv) an admixture of any component(s) stated above. In addition, Claim 4 is indefinite as to the recitation ""a substance" (line 1 of the claim item (B)); does "a substance" is the same substance recited in the line1 of Claim 4? If so, does the said substance refer to "the target substance (sample)" which is "an object of screening" (see the specification, page 27, lines 9-10). In regard to the target substance to be detected, the recitation "...a sample which may contain a substance..." is indefinite because the target substance must be present in the sample of claimed

step 2 (i.e. item (B)) so that the method for detecting the target substance can be established. Note that the target substance is added to a suspension of permeabilized neutrophil cells as an appropriate concentration (see page 27, lines 9-15), i.e. the presence of the substance is known and the absence of the substance is not a case. Thus, "may", a conditional phrase, should be deleted from the claim. Furthermore, Claim 4 is unclear regarding "the subject substance" (see item (C)); to what the recited substance refer? Does the recitation refer to the substance contained in the sample as set forth in item (B) of the claim? Or is "the subject substance" protein or enzyme resides in granule of neutrophils cell (see page 25, lines 23-27)? The dependent claims are also rejected.

Claim 5, item b) recites "or" which renders the claim indefinite because the order of addition of a calgranulin and addition of a water-soluble calcium reagent will result in a different biological effect, e. g. calgranulin has been shown to undergo conformational change upon calcium binding (page 361, third paragraph, left panel of reference by Hessian et al.).

Claim 8 recites "the water-soluble calcium compound is a solution or powder of a compound which ...at a concentration of 100 mM or more when ..."; it is unclear as to whether or not 100 mM is the ending concentration generated by dissolving the compound powder in water or 10 mM molarity concentration refers to both (*a*) the solution as claimed and (*b*) the solution generated by dissolving the compound powder in water. Further, Claim 8 is unclear in the recitation "...the compound contacts with water"; does the recitation refer to incompletely dissolving in water? (note that "contact" does not necessarily refer to dissolution of a chemical compound). The phrase "is dissolved in water" would be clearer.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enhancing elastase secretion (example 1) and lactoferrin secretion (example 2) from human neutrophils via increasing Ca^{2+} -bound calgranulin content (calgranulin A or/and B) and screening a target substance regulating elastase secretion from permeabilized neutrophils by controlling calgranulin A or/and B calcium binding activity (example 3), immunodetecting the calgranulin peptides and preparing permeabilized cells having granule secretion capability, and introducing the calgranulin peptide(s) and water-soluble calcium compound into the cells, does not reasonably provide enablement for all polynucleotide variants or polynucleotide encoded calgranulin peptide variants (mutants) thereof for their capability of modulating (inhibiting or stimulating) neutrophils secretion of the protein, e.g. esterase, which is present in the primary granule (see page 30, lines 15-16), and lactoferrin, which is present in the secondary granule (see page 32, lines 25-26), and for their use in controlling granule secretion associated intimal injury of blood vessels. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims of the instant application indicate that the active form calgranulin polypeptides are mutational variants (see Claims 7 and 14-16). The claims as written encompass

a large number of polypeptides with a large number of possibilities with regard to the structural alteration of the amino acid sequence, e.g. substitution, deletion and insertion. The specification does not appear to have provided any guidance nor working examples of any variants. Thus, it would require undue experimentation of the skilled artisan to envision all variants which will or will not retain full affinity or partial affinity for calcium at least when compared to calcium-binding capacity of full length wild-type calgranulin isoforms A and B (note that calgranulin is a calcium-dependent).

The current application sets forth secretion of neutrophil granule associated with intimal injury of blood vessels which is related to various disease states (see the specification at the bridging pages 19-20 and Claim 11). Applicants are in possession of modulation of calgranulin based secretion by compounds 1-4 (see Table 1, page 36). Applicants are not in possession of controlling secretion of neutrophil granule by any unknown compounds (the target substances), the secretion associated intimal injury of blood vessels and the injury-related disease states (see page 19, lines 23 to page 20, line 17). The present application provides no guidance nor working examples as to how to apply the modulation of the granule secretion by the target substance (compounds) to control blood vessel injury and related disease states, undue experimentation is required to establish methods of screening and obtaining the substance to control blood vessel injury and related disease states.

The application disclosure and claims have been compared per the factors indicated in the decision *in re Wands* 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue.

The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The scope of the claims:

The current invention is directed to controlling calgranulin-based granule secretion of neutrophils and detecting a target substance modulating calgranulin-enhanced granule secretion in neutrophils. The calgranulin level (activity) is set up as a positive control with respect to the target substance (compound) action (see Table 1 data, page 36). Claims 1-3 and 12 are directed to calgranulin-based controlling granule secretion, and Claims 4-10 and 13-16 to detecting a substance regulating the calgranulin-based secretion. Calgranulin activity is therefore essential to practice the claimed methods.

Claims of the instant application indicate that the active form of calgranulin has a peptide an amino acid sequence in which one or more amino acids are deleted, inserted or substituted and binding calcium thereto, and exhibits the activity of increasing secretion of granules of cell lines having secretion capacity (see Claims 3, 7 and 14-16). This includes encompasses numerous mutations of the polynucleotide sequence and the encoded amino acid sequence as variants. The application provides no guidance nor working examples of structural and functional characterization of these variant polypeptides and use thereof. Therefore, the claims as written encompass a large number of polypeptide fragments including (*i*) a large number of

possibilities in respect to the length of polypeptide (see the recitation in the claims "one or more amino acids are deleted) and (*ii*) a large number of mutational variants: substitution, addition, deletion, and structural alterations in any combination of the foregoing mutational types (see the recitation of Claims 3, 7 and 14-16 as to "one or more amino acids are deleted or added...or replaced with other amino acids).

The specification only discloses full length calgranulin isoforms, A or/and B mediated enhancing secretion of a primary granule enzyme; e.g., esterase, or a secondary granule protein, e.g. lactoferrin, (see examples 1 and 2, and figures 1-5). The claims of the present application encompasses a large number of mutational variants but the specification does not disclose how to make the variant polypeptides nor how to use them to enhance secretion of granules from cell lines having granule secretion. Therefore, the variants recited in the current claim language render the claims so broad that the scope of claims is outside the bounds of the enablement provided in the current application and would have resulted in the necessity of undue experimentation.

(2) The nature of the invention:

As stated above, the claims of the current application are directed to numerous variants of polynucleotide fragments and the polynucleotide encoded polypeptide fragments. Some would be nonfunctional; e.g., incapable of binding calcium. Absent the factual evidence to the contrary and without guidance in the specification as to which ones would or would not have been a priori active or inactive, experimentation is undue.

Applicants have not described (so as to enable) all the variants for their biological activity (e.g. calcium capability and calcium binding related function thereof, e.g. promoting

granule secretion etc.) comprising any amino acid sequence having unpredictable mutational alteration(s).

The current application discloses that a combination of calgranulin A and calgranulin B enhances secretion of esterase (present in primary granule, see page 30, line 16) and lactoferrin (present in secondary granule, see page 32, line 26) proteins in human neutrophils (see figures 3 and 6, respectively). Calgranulin A, i.e. MRP-8, and calgranulin B, i.e. MRP-14, are two isoforms of calcium-binding proteins (see page 183 of Propper, C. et al. (1999) *J. Biol. Chem.* 274, 183-189).

Hessian et al. (*Eur. J. Biochem.* (2001) 268, 353-363) has demonstrated that calgranulin A and B form a non-covalently associated heterodimer, designated MRP-8/MRP-14; the heterodimeric complex functions in the cytosol of neutrophils cells circulating in peripheral blood (see especially abstract). Thus, in view of the present application disclosure and the reference by Hessian et al., contribution of the calgranulin A and B heterodimer to the protein secretion of neutrophils is not excluded. Hessian et al. also teach that mutations in the Arg85-Thr87 region of calgranulin B (i.e. MRP-14) (SEQ ID No. 2 encoded polypeptide) affect antibody recognition indicating a conformation change of the protein (see page 359), and that antibody recognition was a direct reflection of calcium binding by MRP-8 or MRP-14 as the presence of calcium was a requirement for all monoclonal antibody reacting with subunit protein (see page 360, the second paragraph of the left panel). Hessian et al. suggests that the mutations influence Ca^{2+}-binding activity of calgranulin. Because the structural variants including conformation and heterodimer-formation alterations are highly variable, retention of the exact biological function of the calgranulin mutants are required in the claims is unpredictable.

Therefore, one of ordinary skill in the art would have been unable to envision which calgranulin variants recited in the instant claims would have properly functioned within the bound of the current claims.

On the other hand, the substance-modulated granule secretion is a complex cellular regulation event where calgranulin activity may also be a direct target of the substance. For instance, the target substances (i.e., compounds) set forth in page 35, lines 14-20 are an organic reagent, N-(4-methoxybenzyl)-N-(4-methoxyphenyl)-7-piperazinylheptyl amine trihydrochloride. When the compound(s) are mixed, *in vitro* with calgranulin protein(s) (note that Claim 4 item B sets forth mixing calgranulin with the target substance [*referring to "or during the step A"*]), calgranulin would undergo denaturation or partial unfolding and be inactive. Because mixing of the compound results in variable activity of the calgranulin, the method of using both calgranulin and the compound to be assayed is unpredictable as to expected activity.

Claim 4 item B) and Claim 11 set forth a step of causing a sample which may contain a substance inhibiting the granule secretion. Since "a substance" as recited is undefined by structure, it includes numerous compounds including organic (e.g., the compounds 1-4 listed in page 35), or inorganic molecules and any biomolecules, one skilled in the art would not have envisioned which compounds are selected to assess the modulation of granule secretion. It is noted that nowhere does the specification define "a substance" nor provide guidance and working examples with regard to (*a*) characterization of the target substance (compound) reaction with calgranulin and any cellular side-effect e.g. cytotoxicity, caused by the compound thereof, (*b*) experimental evidence of how the compound is related to intimal injury of blood vessels (Claim 11), and (*c*) how controlling the secretion of neutrophil granule can be applied to

a gene therapy for the disease states (see the specification, page 20, lines 5-17). Therefore, the claims do not render the current invention enable.

The application recites that secretion of neutrophil granule accounts for intimal injury of blood vessels and such the injury associates with various disease states: e.g., adult respiratory distress syndrome (see the bridging pages 19-20 and claim 11). Since the disclosure sets forth not only a large quantity of calgranulin variant polypeptides as stated above, but also large number of compounds (the target substances) that are subject to assay for their ability of modulating the secretion and use in modulation of the secretion, undue experimentation is required for both the active calgranulin and the target substance suitable for stimulating or inhibiting the secretion in which the calgranulin plays a central role.

(3) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attribute and characteristics that identify any biological active fragment (either the polynucleotide or the polypeptide) for its use, one of skilled artisan is require performing undue experimentation in order to screen, identify and isolate appropriate mutants which have biological activities compared to wild-type polypeptides.

Propper, C. et al. (*J. Biol. Chem.* (1999) 274, 183-189) show that amino acid exchanges of F89A, L95A, and F20A abolish dimerization of calgranulin B/A (see page 186) and teach that the heterodimeric complex is widely regarded as the biologically active form of most S100 proteins (see page 183, the right panel, lines 14-15), suggesting mutations have a great impact of the mutations on calgranulin activities.

Additionally, Ngo *et al.* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure will require guidance (see Ngo *et al.*, 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, pp. 492-495). Given the lack of sufficient guidance and working examples, predicting what changes can be made to the calgranulin protein sequence so that the mutant molecules have improved or at least retain apparent iron-binding capability after substitution, deletion or/and insertion is unpredictable. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the amino acid sequence of a polypeptide determined its structural property, predictability of which amino acid can be deleted or substituted requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence contribute to its structure, which would have been necessary for one skilled in the art to have knowledge of in order to generate and screen for mutants, and analyze biological actives of mutant polypeptides (variants). The disclosure fails to describe the consequence of the variants, i.e. mutants and their use in enhancing or inhibiting granule secretion of neutrophil cells, and the common attributes or characteristics that identify members of the genus. Because the genus is highly variant, the specification needs to provide sufficient guidance to support enabling.

(4) The quantity of experimentation necessary:

In the absence of working examples with regard to the numerous variant sequences, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The quantity

of experimentation would be large and unpredictable. One skilled in the art would be required to carry out an undue experimentation for screening, making and characterizing variants which have desirable activities, e.g. of calcium binding and the calcium-binding associated biological activity, e.g. protein secretion.

Also, one skilled in the art would be required to pre-screening a large quantity of the target substance e.g. organic compounds (see the compounds 1-4, lines 14-20 at page 35) because Claims 4 and 11 set forth the method of detecting "a substance" inhibiting the granule secretion wherein "a substance" represents a genus encompassing numerous compounds including organic, or inorganic compounds and any biomolecules (note that nowhere does in the specification define "a substance"), and because one of skilled in the art would not able to envision which molecules are selected for detecting their potentials of modulating the granule secretion. Thus, an undue experimentation is also required in this regard.

(5) The unpredictability of the art:

Because of the claimed variant polypeptides are a very large number of polypeptide with respect to calgranulins SEQ ID NO: 1 and 2 are highly variant, the invention is unpredictable in the absence of factual indicia to the contrary.

The claims of current application sets froth that "the active form of calgranulin". Hessian et al. teach that functionally, the phosphorylated calgranulin (i.e. MRP-14) display increased calcium-binding activity compared to non-phosphorylated forms (see page 353, the right panel, lines 17-20), i.e. phosphorylation is required for calgranulin to be activated. Since whether or not variants resulted from mutagenesis can be effectively phosphorylated is unpredictable, the active

form of calgranulin is not invariable, the activity of the variants toward granule secretion of neutrophils is unpredictable.

Also, as stated above, the claim setting forth "a substance" encompassing enormous number of compounds to be assayed by the claimed method, because the target substance per as and effect of the substance (compound) on biological activity of the calgranulin is highly variable. Thus, the outcome of detecting the substance of being able to regulate i.e. inhibit the granule secretion is unpredictable as well.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of variant sequences of polypeptide. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a protein-engineer or a cell biologist with several years of experience in cell biology, organic chemistry and molecular biology as well as knowledge in mutagenesis, neurochemistry and medicine; yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable. As exemplified above, the variant proteins fall into unpredictable activities. An unduly level of skill is needed for the skilled artisan in order to identify clones that generate the proteins of desirable biological activities, especially calcium-binding.

In consideration of each of factors stated above, absent factual data to the contrary, the amount and level of experimentation needed is undue.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

October 15, 2002

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600